REMARKS

This Amendment is in response to the Office Action dated **September 11, 2006** in which claims 1-12 have been rejected. The rejections are traversed. Reconsideration is requested

Claims 1-3 have been amended and claims 29-35 are submitted to present further aspects of the invention. Claims 1-12 and 29-35 are now pending. No additional fees are seen to be due. If this is incorrect please charge any additional fees to the undersigned's deposit account identified in the accompanying transmittal letter.

Claim Rejections - 35 U.S.C. § 112 - First Paragraph - Nonenablement

Claims 1-3 and 5-12 have been rejected as non-enabled in the Office Action, asserting that the specification is enabling for a method of inducing differentiation and/or apoptosis of the tumor cells by administration of cyclopamine in case of basal cell carcinomas (BCC's) but not in case of all tumors. The applicant does not agree.

It is emphasized that the method of claim 1 is not directed to any tumor or any tumor cell. Rather, it is directed to a specifically defined type of tumor, that is, a tumor in which Hh/Smo signaling is utilized for inhibition of tumor cell differentiation and for inhibition of tumor cell apoptosis.

Enclosed herewith is a declaration of Dr. Sinan Tas ("Tas"), one of the inventors and an expert in the molecular and cellular mechanisms of aging and of tumorigenesis [Tas, ¶¶1-4 and Exhibit A]. Dr. Tas's testimony [Tas, ¶7] points out that the person of skill in the art, *when informed of the results to be obtained* for the identified class of tumors, has the ability to apply known assays to determine which tumors meet the criteria of claim 1 and to adjust the delivery form and dosage to achieve the claimed result.[1]

Dr Tas further points out [Tas, ¶¶ 8-12] that the specification describes and exemplifies successful applications of the method on several independent tumors and, ***contrary to***

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[1] The applicant is aware that the Office occasionally disregards declarations of inventors for various reasons. Dr Tas' declaration pertains to matters as to which he has intimate knowledge and a high level of skill. Further, when opinions are provided, a detailed explanation of the basis for his opinions is provided. As such, it is submitted that his testimony must be given the respect and weight as that of a qualified expert, both as to the facts related and to the opinions formed therefrom. However, if any portion of his declaration is not given such weight, such portion cannot properly be disregarded. The referenced paragraphs and exhibits of Dr. Tas's declaration are expressly incorporated herein and so, at minimum, must be addressed as part of these remarks.

the assertion on page 3 of the Office Action, on more than one type of tumor (see e.g. page 7, lines 21-25; page 16, line 22 to page 17, line 4; page 17, lines 4-14; Figures 6A, 6B, 6C, 6D). The method was successful each time it was applied, not only on BCC's but also on other types of tumors within the defined tumor category (e.g. trichoepithelioma and melanocytic tumors). All of the exemplified tumors were human tumors and so the described examples are highly relevant to the practice of invention clinically. Dr Tas further points out that microscopic views of the tissue sections are provided in the application that show that the claimed method of treatment causes a massive apoptotic death and removal of tumor cells so as to cause disappearance of tumor nodules to leave behind cystic spaces with no tumor cells. All of this is shown in the application to be achieved while sparing normal tissue cells (including those with stem and progenitor cell features). Statistically significant data is presented in the application. Dr Tas identifies multiple locations in the specification [Tas, ¶12, Table 1] which explicitly teach that the described method of treatment has utility in treatment not only of the BCC's but also of all those specific tumors that employ the Hh/Smo signaling for inhibition of apoptosis and/or for inhibition of differentiation of tumor cells.

Objective evidence of enablement is also provided. Independent scientific investigations published after the present invention confirm that cyclopamine or a derivative thereof can be utilized for obtaining the technical effects recited in claim 1 on non-BCC tumor cells [Tas, ¶¶ 13-16, and Exhibits J-Q]. These independent investigations include treatments of various types of tumor, including internally located tumors treated by a systemic mode of administration of cyclopamine or a derivative thereof, but the techniques are those mentioned in the present application. The information from these studies is therefore confirmatory of the application.

Regarding the assertion on pages 5-6 of the Office Action, that *Sanchez et al*, *Mechanisms of Development* 2005; 122:223-230, demonstrates that inducing differentiation and/or apoptosis is highly unpredictable, such assertion is incorrect [Tas, ¶14]. *Sanchez et al*, confirms what is taught in the specification of present application, namely, induction of apoptosis of the tumor cells that are defined in claim 1 is dependent on the quantity and duration of application of cyclopamine. See page 228, second column. As such, *Sanchez et al* demonstrates that the application is correct in explicitly teaching that sub-optimal dosage may not produce differentiation and/or apoptosis of the tumor cells (see *e.g.* application, page 18, line 24 - page 19 line 4).

Pages 6-7 of the Office Action refer to applicant's previously filed responses where findings of scientific investigations on the effects of various inhibitors and upregulators of Hh/Smo signaling on various cell types are cited. It is correctly quoted in the Office communication that "responses of cells to cyclopamine in terms of both cellular differentiation and apoptosis depend, indeed, on the cell types, the environment in which the cells reside as well as on the means, extent and duration of the inhibition of Hh/Smo signaling." However, the pending claims are not directed to a method to be applied on any cell type for the attainment of the technical effects described therein. The object cells are particular tumor cells that are clearly defined in claim 1. The environment of tumor cells (*in vivo*) as well as the method to be applied are clearly described. Results with several human tumors that are described in specification, as well as those in subsequent scientific publications, show that the technical effects recited in claim 1 are obtained with high predictability when the method is applied on the specific tumor cells described therein.

Finally it is noted that the Office Action is correct at the bottom of page 7 in recognizing that "amounts of cyclopamine that are 'sufficient' to inhibit *Hh/Smo* signaling and cell proliferation of a certain cell type are not, *a priori* sufficient to induce differentiation and/or apoptosis of the same cells." However, the present application contains an essential teaching on this point, not existing in or suggested by the prior art, namely that when dosage is high enough these results can be obtained. This essential difference, backed up by multiple examples in the application and subsequently independently verified as discussed above, both enables the invention as claimed and differentiates the present application from the prior art.

It is thus apparent from the evidence and facts presented above that the pending claims fulfill the enablement requirements of 35 U.S.C. § 112 - first paragraph. Withdrawal of the non-enablement rejection of claims 1-3 and 5-12 is therefore respectfully requested.

Claim Rejections 35 U.S.C. § 112 - First Paragraph - Written Description Requirement

Claims 1-12 have been rejected under 35 U.S.C. § 112 - first paragraph, asserting that claims directed to derivatives of cyclopamine fail to comply with the written description requirement. The applicant does not agree.

The written description requirement is satisfied if the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See generally MPEP 2163 *et. seq*. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Consequently, rejection of an original claim for lack of written description should be rare.

The Office Action asserts that the cyclopamine derivatives can only be determined by testing and so the description is inadequate. The rejection is without merit.

The claims of the present application are not directed to the derivatives *per se*. Consequently the cases cited in the Office Action, *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016 (Fed Cir 1991), are inapplicable. In both of those cases the claims at issue were directed to DNA sequences *per se*. Furthermore, in case of a gene (a complex chemical compound) there is uncertainty as to the characteristics and function of product. For example, alternative splicing of a transcript is a well known means of generating, from the same DNA sequence, gene products with differing characteristics and functional features. However, in the present case there is no uncertainty as to the relevant characteristics and functional features of a derivative of cyclopamine. It is clearly stated to bind specifically to the same biological target as cyclopamine so as to exert the biological effects of cyclopamine that are described in specification.

The claims of the present application are directed to a treatment method. Use of functional biological characteristics to identify constituents employed in a claimed method is a conventional and well accepted claiming practice. Examples of granted US patent with such claims include US 4491634, US 4596825, US 4816446, US 5227405, US 6149902, US 6306618, US 7090985, and US 7109159. The Office Action does not provide a sound basis for imposing a stricter standard of description to the method claimed in the present application than is routinely applied to method claims of other applications.

The specification of present application teaches that molecules can be derived from cyclopamine or synthesized in such a way that they possess related structural features to exert similar receptor binding properties and biological effects as cyclopamine (page 10, lines 8-10). The specification also discloses that the term "derivative of cyclopamine" is used to refer to such a molecule (page 10, lines 10-11) and it provides further information about such a molecule (page 10, lines 8-26). Such a compound binds specifically to the same biological target as cyclopamine to cause inhibition of Hh/Smo signaling and the technical effects described in claim 1. A person skilled in the art has the skill to create cyclopamine derivatives on the basis of this functional information [Tas, ¶¶ 5-6].

The description allows a person skilled in the art to readily identify compounds that can be used in the claimed method and distinguish them from other compounds. These facts demonstrate that the description is more than adequate to establish that the applicant was in fact in possession of the invention of the use of cyclopamine derivative compounds in the claimed method on the effective date of the present application.

In view of the evidence and facts presented above it is clear that claims 1-12 fulfill the written description requirements of 35 U.S.C. § 112 - first paragraph. Withdrawal of this rejection is therefore respectfully requested.

Claim Rejections - 35 U.S.C. § 112- Second Paragraph

Claim 2 has been rejected as indefinite for failing to specify what the proportion is smaller compared to. Claim 2 has been amended, to identify that proportion. Accordingly the ground for rejection has been removed. Withdrawal of this rejection is therefore respectfully requested.

Claim Rejections - 35 U.S.C. § 103

Claims 1-6 and 8-12 have been rejected as obvious from Dudek et al, US 6,291,516 and claim 7 has been rejected as obvious from *Dudek et* al, taken with *Keller et al*, US 5,891,465. The rejections are traversed. *Dudek et al* does not render obvious the invention of claim 1. Hence, *Dudek et al* does not render obvious the invention of any of claims 1-3 or 5-12 and the combination of *Dudek et al* with *Keller et al* does not render claim 7 obvious.

A. Dudek et al's Teachings Taken as a Whole

Dudek et al is an omnibus disclosure pertaining to "regulators" of the hedgehog pathway which includes as "subject compounds," compounds that have opposing regulatory actions on hedgehog signaling [Tas, ¶17]. Consequently, except when a clarification is made (or can be inferred) as to the nature of "subject compounds" to be used for a given condition, ambiguity reigns as to which of the compounds are to be used and what effect may be expected. Relevant to the present invention, *Dudek et al* is particularly uninformative in its teachings concerning the effects of subject compounds on cellular differentiation and survival. Those processes are said to be "affected" or "altered" or "changed" or "controlled" or "managed" or "manipulated" or "modulated" or "regulated" by use of subject compounds.

The Office Action cites *Dudek et al*'s statement that a hedgehog regulator compound may be used " … to regulate … proliferation or other biological consequences of misexpression of, for example, ptc, hedgehog or smoothened" (column 15, lines 60-64). This statement cannot possibly make obvious the subject matter described in the pending claims. Not only do the compounds in *Dudek et al* include compounds exerting effects not specific to hedgehog signaling [Tas Declaration, ¶ 17], the term to "regulate" a function also lacks clarity. For example, a particular function may be "regulated" in the direction of inhibition or in the direction of stimulation and these are the opposite of each other. Furthermore, the term "other biological consequences of misexpression of, for example, ptc, hedgehog or smoothened" is undefined and may mean many different consequences in different cell types and contexts (please see, for example, the reply filed on March 13, 2006 and the documents filed therewith; even the administration of a specific inhibitor of hedgehog signaling can have very different effects on a clearly defined cellular function, e.g. proliferation, in different cell types in an animal).

Likewise, the cited description of *Dudek et al* concerning the bringing about of a "change" or "modulation" of "a differentiated state, survival and/or proliferation of a cell" may mean a change or modulation in the direction of inhibition or induction of a differentiated state. Similarly, it may mean causation of a decrease or increase in the cell survival or proliferation. In other words, such changes or modulations can entail very different, even opposite, end results.

The fact that *Dudek et al* indicates some of the "subject compounds" might have an effect on differentiation or rate of survival tells the skilled person nothing about which compounds will provide what effect on which type of cells and under what conditions. Such statements have no utility to the skilled person, except as an ***invitation to experiment*** with the "subject compounds." It is well established that an obviousness rejection cannot be maintained on an "obvious to try" standard. *In re Fine,* 5 USPQ2d 1596 (Fed. Cir. 1988). Therefore motivating the skilled person to experiment with *Dudek et al*'s subject compounds, of which cyclopamine and related compounds are a small sub-class, does not in any way contribute to a proper analysis of the obviousness of the claimed invention.

Of course, *Dudek at al* does have some unambigous and supported relevant teachings. Such teachings taken as a whole teach away from the claimed invention. Dr Tas's Declaration at ¶18 provides a table of teachings in *Dudek et al* that lead away from the invention claimed, as far as the use of cyclopamine or another specific inhibitor of hedgehog signaling for induction of differentiation. Dr Tas also points out that *Dudek et al* has no teaching that cyclopamine or another specific inhibitor of hedgehog signaling can induce death and removal of tumor cells, and in fact points in the opposite direction [Tas, ¶¶ 19-23]. Importantly, for both *Dudek et al*'s *in vitro* findings reported by at column 63, lines 13-50 and in Figure 2 and for the *in vivo* findings reported at column 63, line 51 to column 64, line 22 and in Figure 3, ***the cells were examined by microscopy. Microscopy ordinarily enables detection of apoptosis, but no causation of cell death is reported.*** Furthermore, the dosage of the systemically administered cyclopamine in the tumor treatment described in *Dudek et al* is ***magnitudes lower*** than that described in independent investigations to provide tumor cell apoptosis *in vivo* (including of the medulloblastoma cells mentioned in *Dudek et al*; see Tas ¶13 and Exhibit J) and it is also ***several folds lower*** than the dosage that was specifically tested and found to be insufficient to cause a detectable apoptosis of the medulloblastoma cells *in vivo* (see Tas ¶13 and Exhibit L).

What is contemplated in *Dudek et al* for tumor treatment is inhibition of tumor growth (see column 64, lines 10-12), and what is shown as the technical effect obtained on tumor cells by use of cyclopamine is an inhibition of proliferation. Nothing in *Dudek et al* leads one to expect that a suitable dosage could produce tumor cell differentiation or apoptosis.

B. A Manipulative Difference from Dudek et al is Recited

The Office Action asserts that *Dudek et al* disclose a method of treating tumors by administering to a patient in need thereof an effective amount of cyclopamine and thus the method described in claim 1 of instant application is not distinguished from that in *Dudek et al.* If this were so the rejection should be for anticipation, not obviousness. It is not so. Claim 1 recites a manipulative difference from Dudek et al's disclosure.

Dudek et al uses cyclopamine or another specific inhibitor of hedgehog signaling to inhibit proliferation of the tumor cells displaying activation of hedgehog signaling and describes causation of an inhibition of tumor growth. However, it is clear that an amount or dosing of cyclopamine or a derivative thereof that may be effective in inhibiting proliferation is not necessarily effective for attaining the technical effects described in claim 1 of present application. The Office Action recognizes this fact at the bottom of page 7.

As taught in the present application [Tas, ¶24], and subsequently in many independent investigations [Tas, ¶¶13-15 and 25], differentiation and/or apoptosis can be achieved using cyclopamine or a cyclopamine derivative compound, but such results may require significantly higher dosages than to achieve inhibition of proliferation.

That a method of treatment stopping administration of cyclopamine at a dosage that suffices to inhibit tumor cell proliferation would not produce detectable apoptosis of tumor cells is documented also by Dr. Tas's analyses of the tumor depicted in Figures 5A-5F of the application [Tas, ¶¶ 26-28]. The tumor, treated topically on its lower half only clearly shows apoptosis under the treated surface decreasing with distance from the surface. On the untreated half of the tumor, apoptosis is negligible although inhibition of proliferation is clearly evident closer to the surface. The difference is demonstrated visually with color photomicrographs [Tas, ¶26, Figures 1A and 1B] and graphically based on Dr. Tas's calculations [Tas, ¶28, Figures 2A and 2B].

The necessity of administering a dosage effective to achieve differentiation and/or apoptosis is explicitly taught in the application. It is not taught in *Dudek et al.* To the contrary, *Dudek et al* teaches that that a minimum dosage that will produce a therapeutic effect is to be used (column 54, lines 42-49; " … start … *at levels lower than that required … and gradually* *increase the dosage until the desired effect is achieved*"). As already noted with regard to the desired effect of administering cyclopamine to a tumor, the expected effect is inhibition of tumor cell proliferation and thereby inhibition of tumor growth (*Dudek et al* col. 64, lines 10-12). Hence it is clear that *Dudek et al*, seeing an inhibition of proliferation/growth effect, stops before a dosage is obtained that causes differentiation and apoptosis, and teaches the skilled reader to do the same.

In contrast, the present application describes a clear dose-response effect in the attainment of the technical effects described in claim 1 and emphasizes that a suboptimal dosing may not provide said technical effects (see e.g. page 18 line 21 to page 19 line 4 and Figure 7F). Since the claim requires a dosage that produces differentiation and apoptosis there is a clear manipulative difference in the claimed method which distinguishes the claimed invention of claim 1 from Dudek et al's use of cyclopamine on tumor cells.

C. Objective Evidence of Nonobviousness

The manipulative difference produces an unexpected result, the recited tumor cell differentiation and apoptosis. Unlike the situation of anticipation, it is well established that unexpected results are objective evidence of nonobviousness which overcome even a *prima facie* case of obviousness. *United States v. Adams*, 148 USPQ 479 (US SupCt 1966).

Along with *Dudek et al*, teachings already mentioned, the prior art as a whole teaches away from the presently claimed invention. Dr. Tas has provided a table summarizing previously submitted prior art documents in which cyclopamine or a derivative thereof or another specific inhibitor of hedgehog signaling had been applied in prior art on various transformed and tumorigenic cells, and the effects on cell survival/death were evaluated [Tas, ¶29, Table III]. From these documents it is clear that cyclopamine and other specific inhibitors of hedgehog signaling were actually administered in prior art on tumor cells and on the transformed cells displaying constitutive activation of hedgehog signaling, ***but not to an extent that apoptosis was induced***. Thus, ***the skilled person would not even contemplate trying to find conditions where the technical effects described in this invention would be achieved***. [Tas, ¶30].

The general wisdom in the prior art also ran counter to the present invention. Dr. Tas documents other teachings in prior art that would have led the skilled person away from the invention [Tas, ¶31 and Exhibits R and S].

Finally, the invention provides remarkable advantages in tumor treatment, some unique to this treatment. These include the sparing normal cells, especially normal cells having the attributes of stem or progenitor cells; the ability to remove or shrink tumors of patients for whom surgical removal of tumor may not be feasible and the much less severe inflammatory response which apoptotic death provides relative to treatments that cause necrotic cell death [Tas, ¶32].

On the basis of the objective evidence it is submitted that the invention as a whole would not be obvious even if *Dudek et al* had made out *prima facie* obviousness.

D. New Claims

New claims 29-30 depend from claim 1 and are patentable at least for the same reasons given above. Additionally these claims pertain specifically to a human. *Dudek et al* does not treat a human tumor. Further, claim 30 recites observation during administration which is continued until apoptosis is observed. *Dudek et al* does not observe apoptosis and so does not meet this recitation.

Regarding claims 30-35, *Dudek et al* does not teach to administer a compound in an amount specifically sufficient to induce tumor cell apoptosis. Further regarding claims 32 and 34, *Dudek et al* does not treat a human tumor.

E. Conclusion on Obviousness

Consideration of the whole of the *Dudek et al* disclosure, as well as of the entire prior art shows clearly that the invention described and claimed in the present application, is novel, highly surprising and a highly advantageous solution to long-standing problems in tumor therapy. The invention is nonobvious. Withdrawal of the obviousness rejections is respectfully requested.

Conclusion

In view of the foregoing amendments and remarks the outstanding rejections are seen to have been overcome. The invention of all of the claims is enabled; the written description appropriately supports the claims; claim 2 has been made definite; and the subject matter of the claims has been shown to be nonobvious over the *Dudek et al* and *Keller et al* disclosures. Accordingly withdrawal of the outstanding rejections and allowance of the application is respectfully requested.

Respectfully submitted,
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